

Dean L. Engelhardt, et al.

Serial No.: 08/486,069

Filed: June 7, 1995

Page 2 [Communication (Following Applicants' August 11, 1999 Eighth Supplemental Amendment) - September 7, 1999]



### REMARKS

Claims 284-568 are presently pending and under examination in this application. No changes to the claims or the patent specification are being made in this Communication, the purpose of which is to submit information in the form of scientific papers relating to the modification of purine bases at the N-7 position, a so-called "non-Ward" position.

In their previous August 11, 1999 Eighth Supplemental Amendment, Applicants addressed the matter of modifying the non-Ward base positions in the following four portions:

Page 32, beginning with the section titled "Specification Amendments," and continuing through Page 33, first paragraph;

Footnotes 1 and 2 on Pages 32 and 33;

Page 36, last paragraph, in the section titled "New Claims," and continuing through Page 37, first paragraph; and

Page 38, first two paragraphs, in the section titled "Base Modifications"

In the last-cited portion (first two paragraphs on page 38), Applicants wrote:

#### Base Modifications

In the August 3, 1999 Examiner Interview Summary Record, it was indicated that "We discussed whether there was, and of what scope, the support for base modifications at other than Ward [modification] positions. The new matter [rejections] in the action mailed 1/6/98, are deemed overcome."

As discussed above, the non-Ward base modification positions were disclosed in originally filed claims 12, 15, 16, 17, 18 and 20 (recited in footnote 1 above). Further elaboration of these positions was made in Applicants' May 1, 1999 Fourth Supplemental Amendment. See pages 48, through the first paragraph on page 51 of that paper. See also Exhibits 5-16 referenced on pages 48-50.

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In addition to those last remarks above and the information cited therein, Applicants would like to respectfully point out that modifications to the N-7 position of purines were known in the art at the time their application was first filed in June 1982. Illustrative of such knowledge are the disclosures listed below and submitted herewith as Exhibits A-E:

Yamamoto, O., "Adenine-N-oxide produced from adenine with gamma-rays and its binding to SH protein," J. Radiation Research 21:239-247 (1980) [Exhibit A];

Rhaese, H.-J., "Chemical Analysis of DNA Alterations: III. Isolation and Characterization of Adenine Oxidation Products Obtained from Oligo- and Monodeoxyadenylic Acids Treated with Hydroxyl Radicals," Biochimica Et Biophysica Acta 166:311-326 (1968) [Exhibit B];

Taylor, M. R., "Metal Binding to Nucleic Acid Constituents. The Crystal Structure of Trichloroadeninumzinc(II)," Acta Crystallogr. B29:884-890 (1973) [Exhibit C];

Walker et al., "The Interaction of H<sup>+</sup>, Zn<sup>2+</sup>, and Cu<sup>2+</sup> With Adenine And Guanine," Australian Journal of Chemistry 26:2391-2399 (1973) [Exhibit D]; and

Srinivasan et al., "X-Ray Crystal Structures of Zinc-Adenine and Zinc-Guanine Complexes," J. of Chemical Society D24:1668-1669 (1970) [Exhibit E].

The first two above-listed articles (Exhibits A and B) concern oxidation of the N-7 position of the purine whereas the last three articles (Exhibits C-E) relate to the attachment of metal complexes, principally zinc, to the N-7 purine position.

The Examiner is respectfully invited to consider the information contained in these five articles (Exhibits A-E) as they relate to the Applicants' presently claimed invention.

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Favorable action on the pending claims of record is respectfully  
requested.



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**SUMMARY AND CONCLUSIONS**

Claims 284-568 are pending and continue to be presented for examination in this application. No amendments either to the specification or the claims have been made above.

No fee is believed due for filing this Communication. If any fee or fees are due in connection with filing this Communication, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Ronald C. Fedus".

Ronald C. Fedus  
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Attorney for Applicants

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<u>Authors</u>	<u>Publication Title</u>	<u>Enzo's Product</u>	<u>Exhibit</u>
Guilford et al.	"Identification of a Cancer Susceptibility Gene using the LI-COR 4000L"	IRD800	D
Esser et al.	"Direct Fluorescent Labeling and Automated Analysis of Genomic Clones for Mapping"	IRD700 IRD800	E
Roemer et al.	"Advances in Near-IR Fluorescence Automated DNA Sequencing, New Dyes, Optics and Multiplex Scanning"	IRD700	F

Finally, attached to this Communication as Exhibit G is an October 23, 1997 news release by Enzo Biochem, Inc. announcing that it will produce and supply its proprietary DNA labeling and detection reagents and kits to be used in conjunction with Li-Cor's automated DNA sequence analysis systems.

Applicants invite consideration of the sequencing product information and publications set forth in attached Exhibits A-G.

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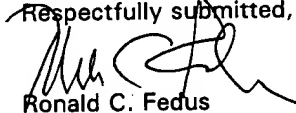
### SUMMARY AND CONCLUSIONS

No claims have been amended, added or canceled by this Communication. Claims 284-512 continue to be presented for further examination in this application.

No fee or fees are believed due for filing this Communication, the purpose of which is to submit information relating to the present Assignee's sequencing products in the form of attached Exhibits A-G. In the event, however, that any fee or fees are due, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

  
Ronald C. Fedus  
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### REMARKS

The purpose of this Communication is to present some information relating to nucleic acid sequencing products and equipment which were commercially available at the time Applicants' first application in this family was filed in June 1982.

Among the commercially available products and equipment for sequencing nucleic acids before June 1982 were those listed below and sold and marketed by the following four companies:

Bethesda Research Laboratories, Inc. (BRL) of Rockville, Maryland;  
Miles Laboratories - Research Products Division of Elkhart, Indiana;  
New England Nuclear (NEN) of Boston, Massachusetts, and  
PL Biochemicals, Inc. of Milwaukee, Wisconsin.

#### Bethesda Research Laboratories (BRL)

Rockville, Maryland

<u>Name of Product/Equipment</u>	<u>Source</u>	<u>Exhibit</u>
BRL Sequencing Gel Electrophoresis System BRL #1030	Bethesda Research Laboratories, Inc. 1979 Catalog	A
BRL #1030	<u>Nature</u> advertisement January 18, 1979 (cover 3 & page vii)	B
Sequencers Model SO (Maxam-Gilbert)	<u>Nature</u> advertisement November 22, 1979 (page viii)	C
The Sequencers (two models: 34 X 40 cm 30 - 85 cm adjustable format)	<u>Nature</u> advertisement January 1, 1981 (page ii)	D
The Sequencers	<u>Nature</u> advertisement January 22, 1981	E

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Miles Laboratories, Inc. - Research Products Division

Elkhart, Indiana

Canalco HSG Chamber	<u>Nature</u> advertisement January 18, 1979 (unmarked page)	F
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New England Nuclear (NEN)

Boston, Massachusetts

DNA Sequencing NEK-010	<u>Nature</u> advertisement August 20, 1981 (unmarked page)	G
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DNA Sequencing System	<u>Nature</u> advertisement March 19, 1982 (page 1447)	H
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PL Biochemicals, Inc.

Milwaukee, Wisconsin

M13 Cloning/Sequencing Kit No. 1510	<u>Science</u> advertisement November 20, 1981 (entire page 215)	I
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It should be pointed out that all of the above-listed commercial nucleic products and equipment for sequencing nucleic acids were based upon the use of then conventional radioactive labeling, notably  $^{32}\text{P}$ . With the advent of Applicants' present sequencing invention as set forth in the presently pending sequencing claims, the use of chemically modified nucleotides for marking fragments in sequencing procedures became a reality. In addition to filling a long felt need in the sequencing arts for better nucleic acid labeling and detection, thereby supplanting previous sequencing methodology based upon radioisotopic labeling, the present invention has achieved widespread acceptance and unparalleled commercial success by others in the sequencing field.

Applicants invite consideration of any or all of the commercial information listed and attached as Exhibits A-I.

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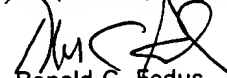
### SUMMARY AND CONCLUSIONS

No claims have been amended, added or canceled by this Communication. Claims 284-512 as previously pending in Applicants' June 3, 1999 Six Supplemental Amendment continue to be presented for further examination in this application.

No fee or fees are believed due for filing this Communication. In the event, however, that any fee or fees are due, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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